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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.,
Petitioner,

v.

BIOGEN MA INC,
Patent Owner.

Case IPR2018-01403
Patent No. 8,399,514 B2

Before SHERIDAN K. SNEDDEN, JENNIFER MEYER CHAGNON, and JACQUELINE T. HARLOW, *Administrative Patent Judges.*

SNEDDEN, *Administrative Patent Judge.*

DECISION
Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

Mylan Pharmaceuticals Inc. ("Petitioner" or "Mylan"), filed a Petition requesting an *inter partes* review of claims 1–20 of Patent No. 8,399,514 B2 (Ex. 1001, "the '514 patent"). Paper 2 ("Pet."). Biogen MA Inc. ("Patent Owner" or "Biogen") filed a Preliminary Response. Paper 7 ("Prelim. Resp.").

With prior authorization, Petitioner filed a Reply to Patent Owner's Preliminary Response (Paper 9) to address the Federal Circuit's decision in *FWP IP APS v. Biogen MA Inc*., No. 2017-2109, 2018 WL 5292070 (Fed. Cir. Oct. 24, 2018). Patent Owner filed a Sur-Reply. Paper 10.

To institute an *inter partes* review, we must determine that the information presented in the Petition shows "a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). The Supreme Court has held that a decision to institute under 35 U.S.C. § 314 may not institute on less than all claims challenged in the petition. *SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348, 1359–60 (2018) ("*SAS*"). After considering the evidence and arguments presented in the Petition, we determine that Petitioner has demonstrated a reasonable likelihood of success in proving that at least claim 1 of the '514 patent is unpatentable. Accordingly, an *inter partes* review of all of the claims and all of the grounds presented in the Petition is hereby instituted.

In this Decision, we address all issues raised by the parties in the pre-trial briefing. Our factual findings and conclusions at this stage of the proceeding are based on the evidentiary record developed thus far. This is not a final decision as to the patentability of claims for which *inter partes*

review is instituted. Our final decision will be based on the record as fully developed during trial.

A. Related Matters

The parties identify the following litigation between the parties involving the '514 patent: *Biogen International GmbH v. Mylan Pharmaceuticals Inc*., C.A. No. 17-cv-116-IMK (N.D. W.Va.). Pet. 2; Paper 11, 3. The parties also identify several other litigations involving the '514 patent. Pet. 2–3; Paper 11, 3.

The '514 patent has also been involved in the following proceedings before the Patent Trial and Appeal Board ("PTAB" or "Board"): *Coalition for Affordable Drugs V LLC v. Biogen MA Inc*., IPR2015-01993; *Coalition for Affordable Drugs V LLC v. Biogen MA Inc*., IPR2015-01136; and *Biogen MA Inc., v. Forward Pharma A/S*, Patent Interference 106,023.

B. The '514 patent

The subject matter claimed in the '514 patent is directed to methods of treating patients needing treatment for Multiple Sclerosis or MS. Ex. 1001, 27:59–30:27. The heart of the treatment, and a requirement of every claim, is administering about 480 milligrams (mg) per day of certain fumarates. *Id.* The fumarates are limited to dimethyl fumarate (DMF), monomethyl fumarate (MMF), or their combination. *Id.* Biogen markets dimethyl fumarate under the tradename Tecfidera®. Prelim. Resp. 1–2. The drug is indicated for the treatment of patients with MS, including relapsing forms of MS (RRMS). Ex. 2003, 7–8.

C. Illustrative Claims

Independent claims 1, 11, 15, and 20, reproduced below, are illustrative of the challenged claims:

> 1. A method of treating a subject in need of treatment for multiple sclerosis comprising orally administering to the subject in need thereof a pharmaceutical composition consisting essentially of
>
> (a) a therapeutically effective amount of dimethyl fumarate, monomethyl fumarate, or a combination thereof, and
>
> (b) one or more pharmaceutically acceptable excipients, wherein the therapeutically effective amount of dimethyl fumarate, monomethyl fumarate, or a combination thereof is about 480 mg per day.
>
> 11. A method of treating a subject in need of treatment for multiple sclerosis consisting essentially of orally administering to the subject about 480 mg per day of dimethyl fumarate, monomethyl fumarate, or a combination thereof.
>
> 15. A method of treating a subject in need of treatment for multiple sclerosis comprising orally administering to the subject pharmaceutical composition consisting essentially of
>
> (a) a therapeutically effective amount of dimethyl fumarate and
>
> (b) one or more pharmaceutically acceptable excipients, wherein the therapeutically effective amount of dimethyl fumarate is about 480 mg per day.
>
> 20. A method of treating a subject in need of treatment for multiple sclerosis comprising treating the subject in need thereof with a therapeutically effective amount of dimethyl fumarate, monomethyl fumarate, or a combination thereof, wherein the therapeutically effective amount of dimethyl fumarate, monomethyl fumarate, or a combination thereof is about 480 mg per day.

D. Evidence Relied Upon

Petitioner relies upon the following prior art references:

Ex. 1005, Biogen News Release, *Phase II Study of Oral Compound BG-12 Meets Primary Endpoint in Multiple Sclerosis* (Jan. 9, 2006) ("Biogen Press Release").

Ex. 1006, S. Schimrigk et al., *A Prospective, Open-Label, Phase II Study of Oral Fumarate Therapy for the Treatment of Relapsing-Remitting Multiple Sclerosis*, 10 (Suppl. 2) MULTIPLE SCLEROSIS CLIN. & LAB. RES. S258, Abstract P642 (2004) ("Schimrigk 2004").

Ex. 1007, L. Kappos et al., *Efficacy of a Novel Oral Single-Agent Fumarate, BG00012, in Patients with Relapsing-Remitting Multiple Sclerosis: Results of a Phase 2 Study*, 253 (Suppl. 2) J. NEUROL. II27, O108 (2006) ("Kappos 2006").

Ex. 1008, International Publication No. WO 2006/0037342 A2 (published Apr. 13, 2006) ("WO '342").

Ex. 1009, R. K. Joshi et al., U.S. Patent No. 7,320,999, issued Jan. 22, 2008 ("Joshi '999").

Ex. 1010, NCT00168701, CLINICALTRIALS.GOV, https://clinicaltrials.gov/archive/NCT00168701/2005_09_14 ("Clinical Trials").

Ex. 1011, ICH Harmonised Tripartite Guideline - *Dose-Response Information to Support Drug Registration E4* (Mar. 10, 1994) ("ICH Guideline").

Petitioner also relies upon the Declarations of Dr. John R. Corboy (Ex. 1002), Dr. Leslie Z. Benet (Ex. 1003), and Dr. Ian McKeague (Ex. 1004 ("McKeague Decl.")) to support its contentions.

E. Asserted Grounds of Unpatentability

Petitioner asserts the following grounds of unpatentability (Pet. 4–5):

Ground	Claims	Basis	References
1	1–20	§ 103(a)	Biogen Press Release and Schimrigk 2004
2	1–20	§ 103(a)	Kappos 2006 and Schimrigk 2004
3	1–20	§ 103(a)	Kappos 2006 and WO ’342
4	1–20	§ 103(a)	Kappos 2006, Clinical Trials, Joshi ’999, and ICH Guideline

F. Abbreviations

DMF	Dimethyl fumarate
BG00012, BG-12, or BG12	Dimethyl fumarate
BID	Twice daily
EDSS	Expanded disability status scale
EMA	European Medicines Agency
MMF	Monomethyl fumarate
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
RRMS	Relapsing-remitting multiple sclerosis
TID	Three times daily

II. PETITIONER’S UNPATENTABILITY GROUNDS

A. Claim Construction

For petitions filed before November 13, 2018, we interpret the claims of an unexpired patent that will not expire before issuance of a final written decision using the broadest reasonable interpretation in light of the specification. *See* 37 C.F.R. § 42.100(b) (2016); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016). Under the broadest reasonable

construction standard, claim terms are presumed to have their ordinary and customary meaning, as would be understood by one of ordinary skill in the art in the context of the entire disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Only terms that are in controversy need to be construed, and then only to the extent necessary to resolve the controversy. *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999).

Petitioner submits that none of the terms in the claims of the '514 patent require construction and, instead, all terms take on their plain meaning. Pet. 17. At this stage of the proceeding, Patent Owner does not present any alternative claim construction arguments.

We independently determine that no explicit construction of any claim term is necessary to determine whether to institute a trial in this case.

B. Person of Ordinary Skill in the Art

The person having ordinary skill in the art is a hypothetical person that is presumed to be aware of all the relevant prior art. *Custom Accessories, Inc. v. Jeffrey-Allan Indust., Inc.*, 807 F.2d 955, 962 (Fed. Cir. 1986); *Kimberly-Clarke Corp. v. Johnson & Johnson*, 745 F.2d 1437, 1453 (Fed. Cir. 1984). Moreover, the prior art itself is generally sufficient to demonstrate the level of skill in the art at the time of the invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required "where the prior art itself reflects an appropriate level and a need for testimony is not shown") (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985)).

Petitioner asserts that a "person of ordinary skill in the art would have had (1) several years' experience in designing clinical studies to meet regulatory expectations and/or analyzing data from such studies; (2) an advanced degree (PhD, MD, PharmD) and training in clinical pharmacology or experience treating MS; and (3) experience with the administration or formulation of therapeutic agents, their dosing, and the literature concerning drug developmental study and design." Pet. 10–11.

At this stage of the proceeding, and absent opposition from Patent Owner, we adopt Petitioner's definition of the level of ordinary skill in the art for purposes of determining whether to institute a trial.

C. Petitioner's Patentability Challenges

1. Ground 1: Obviousness of Claims 1–20 over the Combination of Biogen Press Release and Schimrigk 2004

a. Summary of References Relied Upon

i. Biogen Press Release

Biogen Press Release reports as follows:

> Biogen . . . and Fumapharm AG today announced that a Phase II study designed to evaluate the efficacy and safety of BG-12, an oral fumarate, in patients with relapsing-remitting multiple sclerosis met its primary endpoint. Treatment with BG-12 led to a statistically significant reduction in the total number of gadolinium-enhancing brain lesions as measured by MRI with six months of treatment versus placebo. This Phase II multi-center, double-blind, placebo-controlled study enrolled approximately 250 patients at sites in 10 countries in Europe.

Ex. 1005; Pet. 36.

Petitioner additionally argues that skilled artisans would have understood that Biogen Press Release reports the results of the study

disclosed by Kappos 2005.[1] Pet. 36 (citing Ex. 1002 ¶ 67; Ex. 1003 ¶ 132). Kappos 2005 describes a six month "randomized, double-blind, placebo-controlled, phase II study being conducted at 45 clinical centers in Europe" where daily dosages of 720 mg, 360 mg, and 120 mg were to be tested for efficacy and safety in RRMS. Ex. 1015, 2.

ii. Schimrigk 2004

Schimrigk 2004 discloses that

> Oral fumarate is an effective and safe therapy for the treatment of psoriasis. Similar to psoriasis, the inflammatory process in multiple sclerosis (MS) is thought to be mediated by a T helper I (THI)-type cytokine reaction due to global immune suppression or a TH2-mediated bystander suppression.

Ex. 1006, 4–5.

Schimrigk 2004 reports the results of a 70-week clinical trial involving the treatment of RRMS with oral fumarate therapy (Fumaderm®). *Id.* at 5. The study consisted of four phases: a 6-week baseline; an 18-week treatment; a 4-week wash-out; and a second 70-week treatment phase. *Id.* Patients received up to 720 mg/day of DMF[2] in the first treatment phase. *Id.* Patients received up to 360 mg/day of DMF in the second treatment phase. *Id.* Schimrigk 2004 discloses that "[o]ral fumarate therapy significantly

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[1] Ex. 1015, L. Kappos et al., *A Randomised, Placebo-controlled Phase II Trial of a Novel Oral Single-Agent Fumarate Therapy, BG00012, in Patients with Relapsing-Remitting Multiple Sclerosis*, 252 (Suppl. 2) J. NEUROL. II/148, P574 (2005) ("Kappos 2005").

[2] According to Petitioner, DMF is the most active component of Fumaderm®. Pet. 37; Ex. 1020; Ex. 1003 ¶¶ 134, 137, 141–145.

reduced the number and volume of [gadolinium enhancing (Gd+)] lesions over 70 weeks of treatment." *Id.* More specifically, Schimrigk 2004 discloses that

> Significant reductions from baseline in the number of Gd+ lesions were observed starting after week 12 of treatment with fumarate ($p < 0.05$). In addition, there were significant reductions from baseline in Gd+ lesion volume starting after week 12 ($p < 0.01$).

Id.

iii. Schimrigk 2004 Poster[3]

According to Petitioner, Schimrigk 2004 Poster concerns the same study disclosed in Schimrigk 2004. Pet. 37. Petitioner contends that Schimrigk 2004, when read in view of Schimrigk 2004 Poster, discloses "that the fumarate therapy was effective to treat MS, describing a 'significant reduction in the number of Gd+ lesions . . . following 18 weeks of oral fumarate treatment, with a further reduction after 70 weeks.'" *Id.* (quoting Ex. 1012, 4).

b. Petitioner's Contentions

Petitioner asserts that claims 1–20 are unpatentable under 35 U.S.C. § 103 as obvious over the combination of Biogen Press Release and Schimrigk 2004. Pet. 34–44. In particular, Petitioner contends that Biogen

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[3] Ex. 1012, S. Schimrigk et al., *A Prospective, Open-Label, Phase II Study of Oral Fumarate Therapy for the Treatment of Relapsing-Remitting Multiple Sclerosis* (2004), available at http://web.archive.org/web/20041021033354/http://www.fumapharm.ch:80/pdf/BG-12_Schimrigk_Poster_Final.pdf ("Schimrigk 2004 Poster").

Press Release discloses that a Phase II study designed to evaluate the efficacy and safety of BG-12 resulted in "a statistically significant reduction in the total number of gadolinium-enhancing brain lesions as measured by MRI." Pet. 36 (citing Ex. 1005). Biogen Press Release does not disclose an effective dosage of BG–12, however, Petitioner contends that a person of ordinary skill in the art would have understood that Biogen Press Release reports the results of a study disclosed in Kappos 2005. Kappos 2005 describes a six month study testing daily dosages of 720 mg, 360 mg, and 120 mg for efficacy and safety in MS. Pet. 36 (citing Ex. 1002 ¶ 67; 1003 ¶ 132); Ex. 1015, 2.

Biogen Press Release, even when read in view of Kappos 2005, does not indicate which of the tested dosages showed efficacy. In this regard, Petitioner directs our attention to Schimrigk 2004 and Schimrigk 2004 Poster and contends that those references show "that DMF doses of 720 mg/day, 360 mg/day, and those in between, such as 480 mg/day, were likely to be efficacious to treat MS." Pet. 36. Specifically, Petitioner contends that "[t]he authors reported that the fumarate therapy was effective to treat MS, describing a 'significant reduction in the number of Gd+ lesions . . . following 18 weeks of oral fumarate treatment, [where 720 mg/day of DMF administered], with a *further reduction* after 70 weeks[, where 360 mg/day of DMF administered].'" *Id.* at 37 (citing Ex. 1012) (emphasis added).[4]

[4] We understand Petitioner's argument to be that the study disclosed by the authors of Schimrigk 2004 showed that oral fumarate treatment was shown

Having identified that DMF was effective in treating MS, Petitioner contends that "[s]killed artisans would have been motivated to take the next obvious drug development step: optimize the dose of DMF, taking into account its known side-effect profile, patient compliance issues arising from three times daily dosing, and general principles of drug development." Pet. 37. Petitioner also contends as follows:

> Given these results and the state of the art, skilled artisans would have been motivated to optimize the dose of what was known to be an effective treatment—a process that is part and parcel of routine drug development. Ex. 1002 ¶¶ 132–154; Ex. 1003 ¶¶ 135–148.
>
> Moreover, skilled artisans would be pursuing DMF dose optimization within an established effective range. Prior art pointed to a range of 360 mg/day to 720 mg/day to treat MS. And skilled artisans had achieved success in treating psoriasis with 480 mg/day, providing a particular motivation to pursue that dose when treating MS. Ex. 1002 ¶¶ 136, 147; Ex. 1003 ¶¶ 38, 75-78, 143. For example, in the 1990s, Nieboer demonstrated that 480 mg/day of DMF administered twice daily is an effective daily dose to treat psoriasis. Ex. 1002 ¶¶ 136, 147; Ex. 1003 ¶¶ 78, 143.

Pet. 32.

Regarding a reasonable expectation of success, Petitioner contends that

> Skilled artisans would have also had a reasonable expectation of success in treating MS with 480 mg/day of DMF. Ex. 1002 ¶¶ 144-149; Ex. 1003 ¶¶ 144–147. Schimrigk had

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to be efficacious for both the first treatment period in which 720 mg/day of DMF administered and for the second treatment period in which 360 mg/day of DMF administered.

> shown efficacy of 360 mg/day and 720 mg/day of DMF administered as Fumaderm®, and the January 2006 Press Release confirms efficacy of DMF monotherapy in treating MS. Ex. 1002 ¶¶ 144–149; Ex. 1003 ¶¶ 144-147. These findings, in light of the knowledge that 480 mg/day of DMF could be used to successfully treat psoriasis, would leave little to the skilled artisan's imagination. Ex. 1002 ¶¶ 137–149; Ex. 1003 ¶¶ 144–147. The data all pointed towards successful administration of 480 mg/day of DMF to treat MS. Ex. 1002 ¶¶ 137–149; Ex 1003 ¶¶ 135–148.

Pet. 38.

c. Patent Owner's Contentions

Patent Owner contends that the asserted references do not support Petitioner's position that a person of ordinary skill in the art would have expected a 360 mg/day dose to be efficacious. Prelim. Resp. 25. Relevant to Ground 1, Patent Owner contends that

> The January 2006 Press Release does not identify any doses of BG-12 at all, much less any results for specific dose groups. **Ex. 1005**, 1. . . . As other pre-filing date documents confirm, the 360 mg/day dose was "not statistically significant versus placebo" for any endpoint. *See, e.g.*, **Ex. 1016**,[5] 1; **Ex. 1046**,[6] 19–22.

Id. at 25–26.

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[5] Ex. 1016, Biogen News Release, *Oral Compound BG-12 Achieves Primary Endpoint in Phase II Study of Relapsing-Remitting Multiple Sclerosis; Treatment with BG-12 Led to Statistically Significant Reductions in MRI Measures* (May 30, 2006).

[6] Ex. 1046, L. Kappos et al., *Efficacy of a Novel Oral Single-Agent Fumarate, BG00012, in Patients with Relapsing-Remitting Multiple Sclerosis: Results of a Phase II Study* (16th Meeting of the European Neurological Society, May 30, 2006), attached as Exhibit C to the

Relevant to each of Petitioner's Grounds, Patent Owner further contends that Petitioner fails to meaningfully address the Phase III trial results establishing unexpected results. Prelim. Resp. 29–31. In particular, Patent Owner contends that the 480 mg/day dose had an unexpected magnitude of efficacy compared to a much higher 720 mg/day dose, which was appreciated by the FDA, European Medicines Agency, and Australia's Therapeutic Goods Administration. *Id.* at 29–30 (citing Ex. 2003,[7] 8 (noting that the 720 mg/day dose "offered no additional efficacy" compared to 480 mg/day); Ex. 1037, 75 ("[c]onsistent statistically significant effects with both doses of BG00012 of similar direction and magnitude were seen across the studies at each 6-month period"); Ex. 2004,[8] 48 ("Efficacy results for the 240 mg TID regimen were generally similar to the 240 mg BID regimen.")).

d. Analysis

The legal question before us, in each of Petitioner's Grounds, is whether discovery of the 480 mg/day dose of DMF in a method of treating multiple sclerosis was the result of DMF dose optimization within an established effective range. Pet. 27–32; Prelim. Resp. 38. In this regard, we recognize that "discovery of an optimum value of a variable in a known

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Declaration of Katherine T. Dawson in Biogen U.S. Patent App. No. 12/526,296 ("Kappos 2006 Presentation").

[7] Ex. 2003, FDA Clinical Review for NDA 204063 (BG-12), Heather Fitter, M.D. (Review Completion Date: 11/08/2012).

[8] Ex. 2004, Australian Government, Department of Health, Therapeutic Goods Administration, *Australian Public Assessment Report for Dimethyl Fumarate, Proprietary Product Name: Tecfidera* (October 2013).

process is usually obvious." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1368 (Fed. Cir. 2007); *see also In re Aller*, 220 F.2d 454, 456 (CCPA 1955) ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."); *In re Boesch*, 617 F.2d 272, 276 (CCPA 1980) ("[D]iscovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art."); *In re Geisler*, 116 F.3d 1465, 1470 (Fed. Cir. 1997) ("'[I]t is not inventive to discover the optimum or workable ranges by routine experimentation.'" (quoting *Aller*, 220 F.2d at 456)).

With regard to Ground 1, the parties do not dispute that 480 mg/day is an efficacious dose. Pet. 59. The parties do not dispute that neither Schimrigk 2004 nor Biogen Press Release discloses 480 mg/day of DMF in the treatment of MS. We understand that the parties do not dispute that Schimrigk 2004 discloses that 720 mg/day DMF was effective for the treatment of MS. However, whether Schimrigk 2004 discloses that the 360 mg/day dose of DMF was effective for the treatment of MS is a factual dispute between the parties. In this regard, Petitioner presents evidence in support of its contention that Schimrigk 2004 discloses efficacy of 360 mg/day and 720 mg/day of DMF administered as Fumaderm® (Pet. 37 (citing Ex. 1012, 4)), and that the Biogen Press Release confirms efficacy of DMF monotherapy generally in treating MS. This evidence includes testimony of Dr. Corboy and Dr. Benet. Ex. 1002 ¶¶ 144–149; Ex. 1003 ¶¶ 133–147. For example, Dr. Corboy testifies that Schimrigk 2004 "suggested a range of effective DMF doses in the treatment of MS from

360 mg/day and 720 mg/day." Ex. 1002 ¶ 147. Dr. Benet testifies that Schimrigk 2004 teaches that "doses of 360 mg/day and 720 mg/day DMF was effective in treating patients with RMMS." Ex. 1003 ¶ 133. Both experts testify that a person of ordinary skill in the art would have likewise expected the 480 mg/day dose of DMF to be similarly effective in view of, *inter alia*, the knowledge that the 480 mg/day dose of DMF was previously successfully used (i.e., safe and effective) to treat psoriasis. Ex. 1002 ¶¶ 139, 147; Ex. 1003 ¶¶ 137, 143–144.

At this stage of the proceeding, we are persuaded that the information presented by Petitioner supports its position that the 720 mg/day dose of DMF was shown to be effective in the treatment of MS. Furthermore, at this stage of the proceeding, we recognize Petitioner's currently unrebutted testimonial evidence that Schimrigk 2004 establishes efficacy at 360 mg/day.

We acknowledge Patent Owner's argument and evidence in support of its position that the 480 mg/day dose had an unexpected magnitude of efficacy compared to a much higher 720 mg/day dose. Prelim. Resp. 29 (citing Ex. 2003, 8; Ex. 1037, 75; Ex. 2004, 48). However, whether unexpected results have been established is a question of fact. *In re Harris*, 409 F.3d 1339, 1341 (Fed. Cir. 2005) (whether an invention produces an unexpected result is a question of fact); *In re Geisler*, 116 F.3d at 1469 (Fed. Cir. 1997) (same). For purposes of deciding whether to institute an *inter partes* review, we view a genuine issue of material fact in the light most favorable to the petitioner. 37 C.F.R. § 42.108(c). Thus, for purposes of this

Decision, we resolve the parties' dispute regarding unexpected results in favor of Petitioner.

As set forth in the discussion of Grounds 3 and 4, below, we determine that Petitioner has shown a reasonable likelihood of establishing that at least one of the challenged claims is unpatentable. Accordingly, we institute trial as to all claims and all grounds presented in the Petition. *See SAS*, 138 S. Ct. at 1359–60. Issues for resolution at trial include whether Schimrigk 2004 establishes efficacy at 360 mg/day, and whether knowledge of efficacy of DMF for the treatment of MS at the 720 mg/day dose and/or 360 mg/day dose would have provided sufficient motivation to a person of ordinary skill in the art to optimize the dose of DMF in the treatment of MS. *See Pfizer*, 480 F.3d at 1368 (The motivation to optimize a range or other variable within the claims may flow from the "normal desire of scientists or artisans to improve upon what is already generally known.").

2. Ground 2: Obviousness of Claims 1–20 over the Combination of Kappos 2006 and Schimrigk 2004

a. *Summary of Additional Reference Relied Upon*

i. Kappos 2006

The relevant portion of Kappos 2006 provides as follows (emphasis added):

> Objective: To determine the efficacy of three dose levels of *BG00012*, a novel oral fumarate preparation, on brain lesion activity as measured by magnetic resonance imaging (MRI) in patients with *relapsing-remitting multiple sclerosis (RRMS).*
>
> Methods: This was a randomised, double-blind, placebo-controlled clinical trial of BG00012 in patients with RRMS. Men and women 18 to 55 years of age were eligible for the study

> if they had a diagnosis of RRMS and an Expanded Disability Status Scale (EDSS) score between 0.0 and 5.0. In addition, patients must have had either ≥ 1 relapse within 12 months prior to randomisation or gadolinium-enhancing (Gd +) lesions on cranial MRI at screening. Patients were assigned to four treatment groups and *received BG00012 capsules 120 mg by mouth (PO) once daily (120 mg/day), 120 mg three times daily (360 mg/day), 240 mg three times daily (720 mg/day), or placebo for 24 weeks*. The treatment period was followed by a 24-week dose-blinded safety-extension period during which all patients received BG00012. The primary end point was the total number of Gd+ lesions over four MRI scans at weeks 12, 16, 20, and 24 (calculated as the sum of the four scans). Secondary end points included the cumulative number of new Gd+ lesions from week 4 to week 24 and the number of new/enlarging T2-hyperintense lesions at week 24. Additional end points included the number of new T1-hypointense lesions at week 24, relapse rate, and disability progression as measured by EDSS.
>
> Results: A total of 257 patients were enrolled in the study; 64 patients each were randomly assigned to receive one of the three BG00012 doses and 65 patients to placebo. *Approximately 90% of patients completed the 24-week treatment period. BG00012 (720 mg/day) significantly reduced the mean number of new Gd+ lesions (the primary end point) compared with placebo.* In addition, BG00012 reduced the cumulative number of new Gd+ lesions, the number of new/enlarging T2-hyperintense lesions, and the number of new T1-hypointense lesions compared with placebo.
>
> Conclusion: BG00012 significantly reduces brain lesion activity, *in a dose-dependent manner*, as measured by MRI in patients with RRMS over 24 weeks of treatment.

Ex. 1007, 27.

b. Petitioner's Contentions

Petitioner asserts that claims 1–20 are unpatentable under 35 U.S.C. § 103 as obvious over the combination of Kappos 2006 and Schimrigk 2004. Pet. 44–48. In particular, Petitioner contends that Kappos 2006 "explicitly discloses that 720 mg/day of DMF monotherapy is an effective MS treatment" and that Kappos 2006 further states that "[DMF] significantly reduces brain lesion activity, in a dose-dependent manner." Pet. 44–45 (citing Ex. 1007, 27).

Additionally, Petitioner contends that a person of ordinary skill in the art would have understood at the time of the invention that the 360 mg/day dose was an efficacious dose. Specifically, Petitioner contends that,

> in May 2006, Kappos presented the results of his research to skilled artisans at a leading neurology conference. Ex. 1046. In his slides, Kappos revealed that the patients who had been treated with 360 mg/day of DMF had baseline disease activity that was markedly higher than those patients receiving 720 mg/day, 120 mg/day, and placebo. Ex. 1002 ¶¶ 178–180; Ex. 1003 ¶¶ 169–170. Skilled artisans would have immediately recognized that when assessing whether the 360 mg/day dose was effective, a correction for the higher baseline disease activity in that group would be necessary. Ex. 1002 ¶¶ 178–180; Ex. 1003 ¶¶ 169–172. Skilled artisans would have at a minimum questioned the efficacy conclusions reported for the 360 mg/day dose, and could have performed easy calculations suggesting that 360 mg/day was efficacious. Ex. 1002 ¶¶ 178–180; Ex. 1003 ¶¶ 169–179.

Id. at 46. Thus, in addition to Kappos 2006 providing the statement that DMF was effective in treating RRMS in a dose-dependent manner, Petitioner contends that a person of ordinary skill in the art would have been aware of the data contained in the 2006 slide presentation by the same author

(Ex. 1046, 8–29) and "would have immediately recognized from the Kappos 2006 slides that MS patients who received 360 mg/day DMF during the study had significantly higher disease activity at the start of the study (baseline) than the patients in the other treatment groups." Pet. 54–55 (citing Ex. 1002 ¶¶ 178–180, 203–204; Ex. 1003 ¶¶ 169–172, 207–209). Petitioner contends that when this flaw is accounted for in the Kappos 2006 phase II study results, a dose response curve becomes apparent. *Id.* at 56–57 (citing Ex. 1036,[9] 6; Ex. 1003 ¶¶ 215-219; Ex. 1004 ¶¶ 24–26); *see also* Ex. 1037,[10] 34 (The 360 mg/day dose "also provided statistically significant results for the primary endpoint."). Thus, according to Petitioner, a person of ordinary skill in the art would have appreciated the flaw in reporting the results of the Kappos 2006 phase II study and would have understood from Kappos 2006 that 360 mg/day was also an efficacious dose. Pet. 58 (citing Ex. 1002 ¶¶ 139–140, 209–211; Ex. 1003 ¶¶ 133–134, 220–222; Ex. 1004 ¶¶ 24, 27–28).

For the same reasons set forth in Ground 1, Petitioner contends that Schimrigk 2004 reports efficacy in RRMS of 360 mg/day DMF. Pet. 45–46.

Petitioner contends that "[w]ith doses of 720 mg/day and 360 mg/day both demonstrating efficacy, skilled artisans would have been motivated to optimize the dose of DMF to account for side effects, patient compliance,

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[9] Ex. 1036, R. Fox et al., *Dimethyl Fumarate to Treat Multiple Sclerosis*, in MULTIPLE SCLEROSIS THERAPEUTICS 387 (Jeffrey A. Cohen et al. eds., 4th ed. 2011) ("Fox/Gold Article").

[10] Ex. 1037, European Medicines Agency, *Assessment Report, Tecfidera* (Nov. 26, 2013) ("EMA Report").

and general drug development design principals . . . ." *Id.* at 45. Petitioner further contends that

> Skilled artisans would have likewise had a reasonable expectation that 480 mg/day would work: 480 mg/day fell between two doses of DMF that had demonstrated efficacy as reported in Kappos 2006 and the Schimrigk 2004 study, and had exhibited efficacy in treating psoriasis. Ex. 1002 ¶¶ 167–177; Ex. 1003 ¶¶ 160–168.

Id.

c. Patent Owner's Contentions

With reference to Kappos 2006, Patent Owner contends that Petitioner improperly relies on post-filing date references to "to rewrite the Phase II trial results." Prelim. Resp. 20 (citing Ex. 1036 and Ex. 1037).[11] Patent Owner contends that

> [w]hile the properties and advantages of an invention illustrating its unexpected results need not be fully known as of the filing date, the inverse is not true: a challenger cannot try to use *later expectations* to dispute the unexpectedness of an *earlier invention's* surprising properties. Rather, unexpected results are

[11] We recognize that both Ex. 1036 and Ex. 1037 are post-filing date art and are thus improperly relied upon to establish what was known at the time of the invention. Nonetheless, we find the references informative on the question of how a person of ordinary skill in the art would have interpreted the data presented in Kappos 2006 and Ex. 1046. Specifically, these references support the position that the conclusion with regard to the 360 mg/day dose of DMF was flawed. Thus, the question becomes would a person of ordinary skill in the art at the time of the invention have recognized that flaw when interpreting the data and developing an understanding of the efficacy of the 360 mg/day dose of DMF, or did the flaw only become apparent at a later time.

> evaluated against the prior art. *Allergan, Inc. v. Sandoz Inc*., 796 F.3d 1293, 1305 (Fed. Cir. 2015) ("unexpected results" are evaluated "*relative to the prior art*" (citation omitted)); *In re Lunsford*, 357 F.2d 380, 385 (CCPA 1966) ("[T]here exists a significant, advantageous, *unexpected difference between appellant's invention and the prior art*, which renders the invention patentable."). As the statute requires, a challenger must prove that an invention was obvious "*before* the effective filing date of the claimed invention." 35 U.S.C. § 103.

Id. at 23.

Patent Owner further contends that "[t]he asserted references also do not support Mylan's position that a POSA would have expected a 360 mg/day dose to be efficacious." *Id.* at 25. Relevant to Ground 1, Patent Owner contends that

> The January 2006 Press Release does not identify any doses of BG-12 at all, much less any results for specific dose groups. **Ex. 1005**, 1. Kappos 2006, meanwhile, describes only the 720 mg/day dose as exhibiting positive results. **Ex. 1007**, 27. As other pre-filing date documents confirm, the 360 mg/day dose was "not statistically significant versus placebo" for any endpoint. *See, e.g.*, **Ex. 1016**, 1; **Ex. 1046**, 19–22.

Id. at 25–26.

Patent Owner further contends that Petitioner fails to meaningfully address the Phase III trial results establishing unexpected results. Prelim. Resp. 29–31. In particular, Patent Owner contends that the 480 mg/day dose had an unexpected magnitude of efficacy compared to a much higher 720 mg/day dose, which was appreciated by the FDA, European Medicines Agency, and Australia's Therapeutic Goods Administration. *Id.* at 29–30

(citing Ex. 2003,[12] 8 (noting that the 720 mg/day dose "offered no additional efficacy" compared to 480 mg/day); Ex. 1037, 75 ("[c]onsistent statistically significant effects with both doses of BG00012 of similar direction and magnitude were seen across the studies at each 6-month period"); Ex. 2004,[13] 48 ("Efficacy results for the 240 mg TID regimen were generally similar to the 240 mg BID regimen.")).

d. Analysis

As in Ground 1, a factual dispute between the parties is whether the 360 mg/day dose of DMF was known at the time of the invention to be efficacious in the treatment of MS. In this Ground, Petitioner relies on the same teachings of Schimrigk 2004 as in Ground 1. Additionally, Petitioner contends Kappos 2006 discloses that DMF is effective in treating MS in a dose-dependent manner and that a person of ordinary skill in the art would have understood, upon review of the data supporting the results disclosed in Kappos 2006 (presented in 2006 (Ex. 1046, Exhibit C)), the 360 mg/day dose as an efficacious dose. Ex. 1002 ¶¶ 178–180; Ex. 1003 ¶¶ 169–179.

We recognize that Patent Owner disputes whether a person of ordinary skill in the art would have interpreted the data supporting the results of Kappos 2006 as Petitioner contends. Additionally, as in Ground 1,

[12] Ex. 2003, FDA Clinical Review for NDA 204063 (BG-12), Heather Fitter, M.D. (Review Completion Date: 11/08/2012).

[13] Ex. 2004, Australian Government, Department of Health, Therapeutic Goods Administration, *Australian Public Assessment Report for Dimethyl Fumarate, Proprietary Product Name: Tecfidera* (October 2013).

we recognize Patent Owner's position that results of the 480 mg/day and 720 mg/day doses in Phase III trials were unexpectedly similar. Prelim. 29–30 (citing Ex. 2003, 8; Ex. 1037, 75; Ex. 2004, 48). Each of these contentions, however, raises genuine issues of material fact best resolved at trial.

As explained above, because we determine that Petitioner has shown a reasonable likelihood of establishing that at least one of the challenged claims is unpatentable based on Grounds 3 and 4, we institute trial as to all claims and all grounds presented in the Petition. *See SAS*, 138 S. Ct. at 1359–60.

3. Ground 3: Obviousness of Claims 1–20 over the Combination of Kappos 2006 and WO '342

a. Summary of Additional Reference Relied Upon

i. WO '342

WO '342 discloses "controlled release pharmaceutical compositions comprising fumaric acid ester(s) as active substance(s)." Ex. 1008, Abstract. WO '342 discloses that the compositions of the invention are suitable for use in the treatment of autoimmune diseases, including multiple sclerosis. *Id.* at 37:25–38:9.

With regard to dosages, WO '342 provides the following guidance:

> The daily dosage of the controlled release pharmaceutical composition according to the invention that is administered to treat a patient depends on a number of factors among which are included, without limitation, weight and age and the underlying causes of the condition or disease to be treated, and is within the skill of a physician to determine. In one aspect of the invention the daily dosage can be e.g. from 240 to 360 mg active substance

> given in one to three doses, in another aspect from 360 to 480 mg active substance given in one to three doses, in another aspect 480 to 600 mg active substance given in one to three doses, in another aspect 600 to 720 mg active substance given in one to three doses, in another aspect 720 to 840 mg active substance given in one to three doses, in another aspect 840 to 960 mg active substance given in one to three doses and in yet another aspect 960 to 1080 mg active substance given in one to three doses.

Id. at 36:13–23.

b. Petitioner's Contentions

Petitioner asserts that claims 1–20 are unpatentable under 35 U.S.C. § 103 as obvious over the combination of Kappos 2006 and WO '342. Pet. 48–50. As in Ground 2, Petitioner relies on Kappos 2006 for its disclosure that the dose of 720 mg/day DMF is efficacious for MS treatment. *Id.* at 48. Additionally, Petitioner contends that WO '342 suggests the use of the 480 mg dose of DMF in the treatment of autoimmune disease, such as MS. *Id.* at 48–49. Specifically, Petitioner contends that

> WO '342 teaches skilled artisans about DMF dosing and efficacy. WO '342 states a "suitable therapeutic response may be achieved by use of a single fumaric acid ester alone such as dimethylfumaric acid." [Ex. 1008,] 5:14–16. WO '342 also discloses that the daily dosage administered to a patient "depends on a number of factors among which are included, without limitation, weight and age and the underlying causes of the condition or disease to be treated, and is within the skill of the physician to determine." *Id*. [at] 38:13–17. That daily dosage is said to include "480 to 600 mg of active substance in one to three doses." *Id*. at 38:19.

Pet. 49.

c. Patent Owner's Contentions

Patent Owner contends that the asserted references do not support Petitioner's position that a person of ordinary skill in the art would have expected a 480 mg/day dose to be efficacious. Prelim. Resp. 25.

Patent Owner further contends that Petitioner fails to meaningfully address the Phase III trial results establishing unexpected results. Prelim. Resp. 29–31. In particular, Patent Owner contends that the 480 mg/day dose had an unexpected magnitude of efficacy compared to a much higher 720 mg/day dose, which was appreciated by the FDA, European Medicines Agency, and Australia's Therapeutic Goods Administration. *Id.* at 29–30 (citing Ex. 2003, 8; Ex. 1037, 75; Ex. 2004, 48).

d. Analysis

As in Ground 1 and 2, a factual dispute between the parties is whether the 360 mg/day dose of DMF was known at the time of the invention to be efficacious in the treatment of MS. Pet. 49. In this Ground, Petitioner relies on the same teachings of Kappos 2006 as in Ground 2. Specifically, Kappos 2006 discloses that 720 mg/day of DMF monotherapy is an effective MS treatment and further discloses that DMF significantly reduces brain lesion activity, in a dose-dependent manner. Ex. 1007, 27. Petitioner additionally presents expert testimony that a person of ordinary skill in the art would have immediately recognized a flaw in the data supporting the results disclosed by Kappos 2006.

When the results of Kappos 2006 indicating that 720 mg/day of DMF monotherapy is an effective, dose-dependent MS treatment are combined with the disclosure in WO '342 suggesting a daily dosage of 480 to 600 mg

of fumaric acid esters in one to three doses for treatment of autoimmune diseases, such as MS (Ex. 1008, 38:19, 39:29), and the knowledge that 480 mg/day DMF exhibited efficacy in treating psoriasis, an autoimmune disease with a similar disease mechanism (Ex. 1002 ¶¶ 167–177; Ex. 1003 ¶¶ 160–168), we are persuaded that Petitioner has shown a reasonable likelihood of demonstrating that skilled artisans would have been motivated to optimize the dose of DMF with a reasonable expectation of success.

We acknowledge Patent Owner's argument and evidence in support of its position that the 480 mg/day dose had an unexpected magnitude of efficacy compared to a much higher 720 mg/day dose. Prelim. Resp. 29 (citing Ex. 2003, 8; Ex. 1037, 75; Ex. 2004, 48). However, whether unexpected results have been established is a question of fact. *In re Harris*, 409 F.3d at 1341 (whether an invention produces an unexpected result is a question of fact); *In re Geisler*, 116 F.3d at 1469 (Fed. Cir. 1997) (same). For purposes of deciding whether to institute an *inter partes* review, we view a genuine issue of material fact in the light most favorable to the petitioner. 37 C.F.R. § 42.108(c). Thus, for purposes of this Decision, we resolve the parties' dispute regarding unexpected results in favor of Petitioner.

Accordingly, on this record, we determine that Petitioner has demonstrated a reasonable likelihood that it would prevail in its assertion that at least claim 1 of the '514 patent is unpatentable as obvious over the combination of Kappos 2006 and WO '342. Issues for resolution at trial include whether a person of ordinary skill in the art would have understood that assessment of the efficacy of the 360 mg/day dose required a correction for the higher baseline disease activity in that group, and that, once

corrected, a dose response curve showing that 360 mg/day was also an efficacious dose becomes apparent. Ex. 1002 ¶¶ 178–180; Ex. 1003 ¶¶ 169–172, 215–219; Ex. 1004 ¶¶ 24, 27–28.

4. Ground 4: Obviousness of Claims 1–20 over the Combination of Kappos 2006, Clinical Trials, Joshi '999, and ICH Guideline

a. Summary of Additional References Relied Upon

i. Joshi '999

Joshi '999 relates to the use of dialkyl fumarates, including dimethyl fumarate (Ex. 1009, 6:16–17, 6:60, 8:19), for preparing pharmaceutical preparations for use in transplantation medicine or the therapy of autoimmune diseases, including multiple sclerosis (*id.* at 1:29, 4:45, 8:15), and pharmaceutical preparations in the form of micro-tablets or micro-pellets containing dialkyl fumarates (*id.* at 1:16–20).

According to Joshi '999:

> The dialkyl fumarates used according to the invention may be used alone or as a mixture of several compounds, optionally in combination with the customary carriers and excipients. The amounts to be used are selected in such a manner that the preparations obtained contain the active ingredient in an amount corresponding to 10 to 300 mg of fumaric acid.
>
> Preferred preparations according to the invention contain a total amount of 10 to 300 mg of dimethyl fumarate and/or diethyl fumarate.

Id. at 4:39–48.

ii. Clinical Trials

Clinical Trials discloses a proposed study of a "Double-Blind, Placebo-Controlled, Dose-Range Study to Determine the Efficacy and

Safety of BG00012 in Subjects with Relapsing-Remitting Multiple Sclerosis." Ex. 1010, 1. The described dose ranges to be tested are essentially the same as the dosages described as having been tested by Kappos 2006. *Id.* at 2. Clinical Trials also states "[a]fter 1 week, Group 3 subjects [who began with 120 mg 3 times/day] who tolerate 120 mg tid (as determined by the subject's tolerance of flushing episodes and gastrointestinal [GI] disturbances) will have their dose increased to 240 mg tid." *Id.* Clinical Trials further states "[d]ose reduction will be allowed for subjects who are unable to tolerate investigational drug." *Id.*

iii. ICH Guideline

ICH Guideline describes guidelines for determining appropriate dosages of pharmaceutical products. According to ICH Guideline:

> Knowledge of the relationships among dose, drug-concentration in blood, and clinical response (effectiveness and undesirable effects) is important for the safe and effective use of drugs *in individual patients*. This information can help identify an appropriate starting dose, the best way to adjust dosage to the needs of a particular patient, and a dose beyond which increases would be unlikely to provide added benefit or would produce unacceptable side effects. . . .
>
> Historically, drugs have often been initially marketed at what were later recognized as excessive doses (i.e., doses well onto the plateau of the dose response curve for the desired effect), sometimes with adverse consequences (e.g. hypokalemia and other metabolic disturbances with thiazide-type diuretics in hypertension). *This situation has been improved by attempts to find the smallest dose with a discernible useful effect or a maximum dose beyond which no further beneficial effects is seen, but practical study designs do not exist to allow for precise determination of these doses*. Further, expanding knowledge

> indicates that the concepts of minimum effective dose and maximum useful dose do not adequately account for individual differences and do not allow a comparison, at various doses, of both beneficial and undesirable effects. Any given dose provides a mixture of desirable and undesirable effects, with no single dose necessarily optimal for all patients.

Ex. 1011, 5 (emphasis added). We understand the "dose-response curve" to represent the relationship of the effect of the drug—beneficial or undesirable—to the dose of the drug. We understand the "plateau of the dose-response curve" to be the portion of the curve in which the increase in the dose does not significantly change the effect of the drug.

Further according to ICH Guideline:

> In adjusting the dose *in an individual patient* after observing the response to an initial dose, what would be most helpful *is knowledge of the shape of individual dose-response curves, which is usually not the same as the population (group) average dose-response curve*. Study designs that allow estimation of individual dose-response curves could therefore be useful in guiding titration, although experience with such designs and their analysis is very limited.
>
> In utilizing dose-response information, it is important to identify, to the extent possible, factors that lead to differences in pharmacokinetics of drugs among individuals, including demographic factors (e.g. *age, gender, race*), other diseases (e.g. renal or hepatic failure), diet, concurrent therapies, or individual characteristics (e.g. *weight, body habitus*, other drugs, metabolic differences).

Id. at 6 (emphasis added).

"The choice of the size of an individual dose is often intertwined with the frequency of dosing." *Id.* at 7.

ICH Guideline teaches that

> [a]ssessment of dose-response should be an integral component of drug development with studies designed to assess dose-response an inherent part of establishing the safety and effectiveness of the drug.

Id.

Following up on discussion on page 7, ICH Guideline further teaches:

> It is all too common to discover, at the end of a parallel dose-response study, that all doses were too high (on the plateau of the dose-response curve), or that doses did not go high enough. A formally planned interim analysis (or other multi-stage design) might detect such a problem and allow study of the proper dose range.

Id. at 10.

Pages 13 and 14 describe guidance and advice for determining dosages.

b. Petitioner's Contentions

Petitioner asserts that claims 1–20 are unpatentable under 35 U.S.C. § 103 as obvious over the combination of Kappos 2006, Clinical Trials, Joshi '999, and ICH Guideline. Pet. 50–53. As in Ground 2, Petitioner contends that Kappos 2006 discloses that 720 mg/day of DMF is an effective MS treatment and concludes that DMF "significantly reduces brain lesion activity, in a dose-dependent manner, as measured by MRI." *Id.* at 51.

Petitioner contends that Joshi '999 discloses treating a patient with MS with a therapeutically effective amount of DMF and notes the existence of gastrointestinal side effects with DMF treatment. *Id.* at 52 (citing Ex. 1009, 5:29–33).

With regard to Clinical Trials, Petitioner contends that

> Clinical Trials describes a two-part study looking at efficacy and safety of 120 mg/day, 360 mg/day, and 720 mg/day of DMF. Clinical Trials states "[a]fter 1 week, Group 3 subjects [who began with 120 mg 3 times/day] who tolerate 120 mg tid (as determined by the subject's tolerance of flushing episodes and gastrointestinal [GI] disturbances) will have their dose increased to 240 mg tid." Ex. 1010 at 2. Clinical Trials further states "[d]ose reduction will be allowed for subjects who are unable to tolerate investigational drug." *Id*.

Id.

Petitioner relies on ICH Guideline for its general guidance in determining appropriate and acceptable drug doses in drug treatments. *Id.* Here, we note that ICH Guideline describes that the importance of the dose response for a drug curve is to "identify an appropriate starting dose, the best way to adjust dosage to the needs of a particular patient, and a dose beyond which increases would be unlikely to provide added benefit or would produce unacceptable side effects." Ex. 1011, 5.

Petitioner contends that, "[i]n light of these references, the Board found that skilled artisans would have had motivation and a reasonable expectation of success in treating MS patients with 480 mg/day of DMF." Pet. 52.

c. Patent Owner's Contentions

Patent Owner contends that the asserted references do not support Petitioner's position that a person of ordinary skill in the art would have expected a 360 mg/day dose to be efficacious. Prelim. Resp. 25.

Patent Owner further contends that Petitioner fails to meaningfully address the Phase III trial results establishing unexpected results. Prelim. Resp. 29–31. In particular, Patent Owner contends that the 480 mg/day dose had an unexpected magnitude of efficacy compared to a much higher 720 mg/day dose, which was appreciated by the FDA, European Medicines Agency, and Australia's Therapeutic Goods Administration. *Id.* at 29–30 (citing Ex. 2003, 8; Ex. 1037, 75; Ex. 2004, 48).

d. Analysis

In this Ground, Petitioner primarily relies on the same teachings of Kappos 2006, as in Grounds 2 and 3. Pet. 50–53. As set forth above, for purposes of this decision, we are persuaded that Kappos 2006 discloses that 720 mg/day of DMF monotherapy is an effective MS treatment and further discloses that DMF significantly reduces brain lesion activity, in a dose-dependent manner. Ex. 1007, 27. Petitioner additionally relies on the disclosure in Joshi '999 for its disclosure of the side effect profile for DMF, relies on Clinical Trials for its disclosure that subjects would be given up to 720 mg/day based on the tolerability of individual patients, and relies on ICH Guideline for its disclosure of general guidance to those developing new drugs or drug treatments in determining appropriate and acceptable drug doses. Pet. 52. With regard to ICH Guideline, such guidance includes acknowledgement that "drugs have often been initially marketed at what were later recognized as excessive doses (i.e., doses well onto the plateau of the dose-response curve for the desired effect)," and that "[t]his situation has been improved by attempts to find the smallest dose with a discernible useful effect or a maximum dose beyond which no further beneficial."

Ex. 1011, 5; Ex. 1002 ¶ 197. Based on this information set forth in the Petition, we are persuaded, on this record, that Petitioner has demonstrated a reasonable likelihood of success in proving that at least claim 1 of the '514 patent is unpatentable. *See e.g.*, *In re Boesch*, 617 F.2d at 276 ("[D]iscovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art.").

We acknowledge Patent Owner's argument and evidence in support of its position that the 480 mg/day dose had an unexpected magnitude of efficacy compared to a much higher 720 mg/day dose. Prelim. Resp. 29 (citing Ex. 2003, 8; Ex. 1037, 75; Ex. 2004, 48). However, whether unexpected results have been established is a question of fact. *In re Harris*, 409 F.3d at 1341 (Fed. Cir. 2005) (whether an invention produces an unexpected result is a question of fact); *In re Geisler*, 116 F.3d at 1469 (Fed. Cir. 1997) (same). For purposes of deciding whether to institute an *inter partes* review, we view a genuine issue of material fact in the light most favorable to the petitioner. 37 C.F.R. § 42.108(c). Thus, for purposes of this Decision, we resolve the parties' dispute regarding unexpected results in favor of Petitioner.

Accordingly, on this record, we determine that Petitioner has demonstrated a reasonable likelihood that it would prevail in its assertion that at least claim 1 of the '514 patent is unpatentable as obvious over the combination of Kappos 2006, Clinical Trials, Joshi '999, and ICH Guideline.

III. PATENT OWNER'S DISCRETIONARY DENIAL ARGUMENTS

A. Discretionary Denial Under 35 U.S.C. § 325(d)

Institution of an *inter partes* review is discretionary. *See Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1367 (Fed. Cir. 2016) (explaining that under 35 U.S.C. § 314(a), "the PTO is permitted, but never compelled, to institute an IPR proceeding"). Our discretionary determination of whether to institute review is guided, in part, by 35 U.S.C. § 325(d), which states, in relevant part:

> In determining whether to institute or order a proceeding under this chapter, chapter 30, or chapter 31, the Director may take into account whether, and reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the Office.

Although we have the authority to decline to institute review on the basis that the same or substantially the same prior art or arguments were presented previously to the Office, the statute does not require that result. Our discretion under § 325(d) involves a balance between several competing interests. "On the one hand, there are the interests in conserving the resources of the Office and granting patent owners repose on issues and prior art that have been considered previously." *Fox Factory, Inc. v. SRAM, LLC*, Case IPR2016-01876, slip op. at 7 (PTAB Apr. 3, 2017) (Paper 8). "On the other hand, there are the interests of giving petitioners the opportunity to be heard and correcting any errors by the Office in allowing a patent—in the case of an *inter partes* review—over prior art patents and printed publications." *Id*. In exercising our discretion under § 325(d), we take into account numerous factors, including the facts of each case, and the

burden on the parties and the Board. *See Becton, Dickinson & Co. v. B. Braun Melsungen AG*, Case IPR2017-01586, slip op. at 17–18 (Dec. 15, 2017) (Paper 8) (informative).

Patent Owner requests that we deny institution of trial under 35 U.S.C. § 325(d) because "the Office has considered and previously rejected substantially the same arguments and references during prosecution and multiple failed challenges before the Board." Prelim. Resp. 32.

For the reasons set forth below, we decline to exercise our discretion to deny institution under 35 U.S.C. § 325(d).

1. Art and Arguments Presented in Prosecution

Relevant to Petitioner's Grounds 1 and 2, Patent Owner argues that the Schimrigk 2006,[14] the full publication following the publication of Schimrigk 2004, was fully considered by the Examiner before allowing the '514 patent claims. Prelim. Resp. 39. Patent Owner provides the following summary of the prosecution history of the '514 patent:

> In its preliminary amendment, Biogen argued that it was "unexpected that the dose of about 480 mg/day DMF was similarly effective compared to the higher dose of about 720 mg/day." Ex. 2015, 10. In support of these statements, Biogen submitted a Rule 132 declaration from Dr. Katherine Dawson, Senior Director of Medical Research at Biogen.[15]

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[14] Ex. 1018, S. Schimrigk et al., *Oral Fumaric Acid Esters for the Treatment of Active Multiple Sclerosis: An Open-Label, Baseline-Controlled Pilot Study*, 13 EUR. J. NEUOL. 604 (2006) ("Schimrigk 2006").

[15] Petitioner omitted many pages from its submitted version of the Declaration of Katherine T. Dawson, M.D. Ex. 1046. Patent Owner provides a complete version of the declaration at Ex. 2015.

> The Examiner agreed that "[t]he unexpected and advantageous results demonstrated for the claimed method relative to the other embodiments that are disclosed in the instant specification are not in dispute." Ex. 2018, 7.5 Nevertheless, the Examiner maintained two obviousness rejections over Joshi '072, the published application corresponding to Joshi '999 and Schimrigk 2006, respectively, based on a legally incorrect position that unexpected results must be documented in the specification. *Id.*, 7-9.
>
> Following Biogen's submission of legal arguments illustrating that evidence of unexpected results need not be fully recognized at the time of filing, as well as another Rule 132 declaration from Dr. Richard Rudick (then employed at the Cleveland Clinic) further supporting the unexpected results of Biogen's 480 mg/day dose, the Examiner allowed the '426 application and the '514 patent issued. Ex. 2019, 18-26; Ex. 2020; Ex. 2023.

Prelim. Resp. 10–11 (emphasis omitted).

Having considered Patent Owner's contentions, we decline to exercise our discretion to deny institution based the art and arguments presented to the Office during the prosecution of the '514 patent claims. As noted above, evidence of unexpected results was presented to the Examiner in a Rule 132 declaration from Dr. Katherine Dawson (Ex. 1046; Ex. 2015). It is the interpretation of the data presented in that declaration that Petitioner challenges in this case. *See* Pet. 54–55 (citing Ex. 1002 ¶¶ 178–180, 203–204; Ex. 1003 ¶¶ 169–172, 207–209) (contending that a person of ordinary skill in the art would have been aware of the data contained in the declaration from Dr. Katherine Dawson (Ex. 1046; Ex. 2015) and "would have immediately recognized from the [data] that MS patients who received 360 mg/day DMF during the study had significantly higher disease activity

at the start of the study (baseline) than the patients in the other treatment groups."). In this regard, whether unexpected results have been established is a question of fact. *In re Harris*, 409 F.3d at 1341; *In re Geisler*, 116 F.3d at 1469. At this stage of the proceeding, resolution of whether the data presented to the Examiner during the prosecution of the '514 patent claims establishes unexpected results is a disputed question of fact, best resolved at trial.

2. Art and Arguments Presented in Prior PTAB Proceedings

a. Biogen MA Inc. v. Forward Pharma A/S, Intf. 106,023 ("FP Interference")

Patent Owner contends that the Board in *FP Interference* found that WO '342 "'does not indicate 480 mg/day is a therapeutically effective dose' with respect to MS or any other disease." Prelim. Resp. 15 (citing Ex. 2030, 22–24 (FP Interference Decision)). Patent Owner contends that the Federal Circuit affirmed this finding in *FWP IP APS v. Biogen MA Inc.*, No. 2017-2109, 2018 WL 5292070 (Fed. Cir. Oct. 24, 2018). *See id.* at 14 ("[WO '342] does not teach the key limitation of the count: the 480 mg daily dosage.").

The court also referenced the unexpected results demonstrated in Patent Owner's Phase III clinical trials, in which Patent Owner allegedly discovered,

> *unexpectedly*, that [480 mg/day] had a similar efficacy to the much higher dosage of 720 mg/day. This discovery—by Biogen—was significant because it allowed patients to take lower doses of the medication, which is important in treating a chronic disease like MS.

Prelim. Resp. 15–16.

With regard to the *FP Interference*, Petitioner contends that the disputed issue in that case was written description, not obviousness or unexpected results. Paper 9, 1. Petitioner further contends that

> Different records often lead to different results. Here, not only are the records different, the substantive law is too. Biogen should not be allowed to bootstrap dicta from the Federal Circuit's decision in a case involving different evidence and legal issues to argue for non-institution of *inter partes* review.

Id. at 3.

Upon considering the respective positions of the parties, we decline to exercise our discretion to deny institution based on the Board's previous consideration of WO '342 under a written description analysis. As stated in the *FP Interference* Decision, WO '342 "may show that the claimed subject matter, when considered with the prior art, might have been obvious to one skilled in the art," even if it does fail to adequately describe the claimed subject matter under 35 U.S.C. § 112. Ex. 2030, 28; *see also Regents of Univ. of Calif. v. Eli Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997); *Lockwood v. American Airlines Inc.*, 107 F.3d 1565, 1571–72 (Fed. Cir. 1997). As it is legally possible for a prior art reference to render claimed subject matter obvious even if the reference does not provide § 112 written description support for that same subject matter, we are not persuaded on this record to deny institution of *inter partes* review in this case over the art and arguments previously presented in *FP Interference*.

b. Coalition for Affordable Drugs V LLC v. Biogen MA Inc., IPR2015-01136 ("Coalition I")

Patent Owner asserts that the Petitioner in *Coalition I* unsuccessfully asserted obviousness in view of the following asserted grounds:

Ground	Claims	Basis	References
1	1–20	§ 103(a)	Kappos 2005 and ICH Guideline
2	1–20	§ 103(a)	Clinical Trials and ICH Guideline
3	1–20	§ 103(a)	Prior art admissions and ICH Guideline

Prelim. Resp. 13–14. Patent Owner contends that

> The unsuccessful *Coalition I* grounds significantly overlap with Mylan's proposed grounds in the Petition. Pet., 4–5. Mylan asserts Clinical Trials and ICH Guideline in Ground 4. *Id.*, 5. In Grounds 1 and 2, Mylan also asserts Schimrigk 2004, which is a quarter-page abstract containing less disclosure than Schimrigk 2006, a full seven-page article concerning the same Fumaderm® study. *Id.*, 4. Kappos 2005 concerns the same Biogen Phase II trial as the quarter-page Kappos 2006 abstract that Mylan cites as its lead reference in Grounds 2–4. *Id.*, 4-5.

Prelim. Resp. 14.

We have considered Patent Owner's contentions, and although there is some overlap of prior art references, we do not discern that the Petition presents substantially the same prior art or arguments previously considered by the Office in *Coalition I* sufficient to persuade us to exercise our discretion under 35 U.S.C. § 325(d). For example, Kappos 2006 has a highly relevant and significant teaching not present in Kappos 2005. Compare the (1) "Results" in Kappos 2006, which states that BG00012 at 720 mg/day significantly reduced Gd+ lesions, with (2) the "Results" in Kappos 2005 detailing only what a paper based on tests might reveal.

Furthermore, none of Petitioner's Grounds relies solely on the combination of Clinical Trials and ICH Guideline.

We have taken into account the differences in prior art cited and relied upon in *Coalition I* vis-à-vis the different prior art cited and relied upon in this case. In view of those differences, we are not persuaded to exercise our discretion to deny institution under 35 U.S.C. § 325(d) in view of the art and arguments previously presented in *Coalition I*.

c. Coalition for Affordable Drugs V LLC v. Biogen MA Inc., IPR2015-01993 ("Coalition II")

Patent Owner asserts that the Petitioner in *Coalition II* unsuccessfully asserted obviousness in view of the following asserted grounds:

Ground	Claims	Basis	References
1	1–6, 8–16, 20	§ 103(a)	Kappos 2006, Clinical Trials, Joshi, and ICH Guideline
2	7	§ 103(a)	Kappos 2006, Clinical Trials, Joshi '999, ICH Guideline, and Joshi '992
3	17–19	§ 103(a)	Kappos 2006, Clinical Trials, Joshi '999, ICH Guideline, and Begleiter

Prelim. Resp. 16–19.

Patent Owner contends that Petitioner's "Ground 4 *identically copies* the first ground from *Coalition II*." *Id.* at 17 (citing Pet. 5). Patent Owner contends that in *Coalition II*, Patent Owner "provided extensive objective evidence of nonobviousness, including unexpected results." *Id.* at 18.

Petitioner does not deny that Patent Owner has previously presented to the Office evidence of nonobviousness, including evidence of unexpected

results. Rather, Petitioner contends that the new evidence it presents challenging whether the claimed 480 mg/day dose yields unexpected results has not been rebutted sufficiently. Specifically, Petitioner contends as follows:

> During the previous IPR, the Board noted that it upheld the claims as patentable based solely on its finding of unexpected results because petitioner responded to Biogen's evidence with a single sentence: "As demonstrated above, success was expected, not unexpected." Final Written Decision at 25 (quoting Pet. Reply, Paper 46 at 24). The Board thus noted that "Biogen's expert testimony on this point stands unchallenged." *Id*. So too during prosecution. Biogen submitted declarations from Drs. Rudick and Dawson, and no counter evidence was permissible.
>
> Here, Petitioner submits the declarations of Drs. John Corboy, Leslie Benet, and Ian McKeague, relying on new art and new arguments, and explaining why Patent Owner's unexpected results evidence does not overcome a *prima facie* case of obviousness. Because this evidence is now before the Board, this Petition warrants consideration.

Pet. 62.

Upon considering the respective positions of the parties, we find Petitioner to have the better position. The final written decision in *Coalition II* clearly states that the petitioner in *Coalition II* did not submit rebuttal evidence to counter Patent Owner's evidence of unexpected results in that proceeding, therefore leading to the panel's acceptance of Patent Owner position of unexpected results. Specifically, the Board in *Coalition II* stated as follows:

> Petitioner's Reply *does not effectively address Biogen's unexpected results argument and evidence*. Petitioner responds

> only with a single sentence: "As demonstrated above, success was expected, not unexpected." Pet. Reply, Paper 46, p. 24. Biogen's argument, however, is not merely that it would have been unexpected that some lower doses would have been an effective therapeutic treatment. Rather, Biogen's position is that the magnitude of the clinical efficacy at the specifically claimed dose of about 480 mg/day would have been unexpected. Biogen Res., Paper 38, pp. 43-49. *Petitioner has not directed us to evidence, or provided a reason, for us to doubt the unrebutted testimony* of Biogen's highly qualified and credible experts. *Biogen's expert testimony on this point stands unchallenged*.
>
> * * *
>
> We find the degree of efficacy of the 480 mg/day dose of DMF would have been unexpected.

Ex. 2038, 25.

In view of the above excerpt, we are persuaded by Petitioner's arguments that the express language from the final written decision in that case suggests that the Board considered Patent Owner's evidence to be unrebutted. Accordingly, we decline to exercise our discretion to deny institution in view of *Coalition II*.

B. Discretionary Denial Under 35 U.S.C. § 314(a)

Alternatively, Patent Owner requests that we deny institution of trial under 35 U.S.C. § 314(a), pursuant to the doctrine of *General Plastic Industries Co. v. Canon Kabushiki Kaisha*, Case IPR2016-01357, Paper 19 (PTAB Sept. 6, 2017) (precedential), in view of other previously filed petitions and an interference proceeding involving the '514 patent, identified in Section I.A hereinabove. Prelim. Resp. 48–51.

In *General Plastic*, the Board identified seven nonexclusive factors that bear on the issue of whether the Board should invoke its discretion to

deny institution of an *inter partes* review, based on a follow-on petition on the same patent, under 35 U.S.C. § 314(a) and 37 C.F.R. § 42.108(a):

1. Whether the same petitioner previously filed a petition directed to the same claims of the same patent;
2. Whether at the time of filing of the first petition the petitioner knew of the prior art asserted in the second petition or should have known of it;
3. Whether at the time of filing of the second petition the petitioner already received the patent owner's preliminary response to the first petition or received the Board's decision on whether to institute review in the first petition;
4. The length of time that elapsed between the time the petitioner learned of the prior art asserted in the second petition and the filing of the second petition;
5. Whether the petitioner provides adequate explanation for the time elapsed between the filings of multiple petitions directed to the same claims of the same patent;
6. The finite resources of the Board; and
7. The requirement under 35 U.S.C. § 316(a)(11) to issue a final determination not later than 1 year after the date on which the Director notices institution of review.

General Plastic, slip op. at 15–16 (citing *NVIDIA Corp. v. Samsung Elec. Co.*, Case IPR2016-00134, slip op. at 6–7 (PTAB May 4, 2016) (Paper 9)). In applying these factors, we consider not only the congressional intent that *inter partes* review proceedings provide an effective and efficient alternative to district court litigation, but also the potential for abuse of the review process through repeated attacks by the *same petitioner with respect to the same patent*. *See General Plastic*, slip op. at 18 n.14 (citing H.R. Rep. No. 112-98, pt. 1, at 48 (2011) ("Allowing similar, serial challenges to the same

patent, by the same petitioner, risks harassment of patent owners and frustration of Congress's intent in enacting the Leahy-Smith America Invents Act").

In this case, Patent Owner acknowledges that Petitioner is not a petitioner on any previously filed petitions involving the '514 patent. Prelim. Resp. 49. Patent Owner further acknowledges that *General Plastic* involved follow-on petitions by the same petitioner. *Id.* Nonetheless, Patent Owner asks that we expand *General Plastic* to a new petitioner because, according to Patent Owner, the Petition here is similar to previously-filed *inter partes* review petitions and co-pending litigations involving the '514 patent. *Id.* at 49–50.

Additionally, Patent Owner contends that "an exercise of discretion is appropriate to conserve the Board's resources, because [Petitioner] has asserted the same unpatentability arguments in co-pending district court litigation that will reach trial at essentially the same time that the Board will reach its one-year statutory deadline for a final written decision if this IPR is instituted." *Id.* at 49.

Petitioner contends that "[t]his petition presents new unexpected results evidence, new arguments, and new prior art references not previously considered and not previously before the Patent Office during prosecution." Pet. 61. Petitioner further contends that "[i]t would be particularly harsh to deny institution where, as here, the Board has previously found the claims *prima facie* obvious, but upheld their patentability based on the total failure of a previous, unrelated petitioner to submit any arguments or evidence whatsoever on unexpected results." *Id.* at 62.

Upon considering the respective positions of the parties and the factors set forth *General Plastic*, we decline to exercise our discretion under 35 U.S.C. § 314(a) to deny institution in this case. We also are not persuaded that the co-pending district court litigation warrants denial of *inter partes* review here. In this regard, we note that the Petition was filed within the one year time period set by statute (*see* 35 U.S.C. § 315(b)), and Patent Owner does not allege this *inter partes* review is barred by any civil action filed by Petitioner (*see* 35 U.S.C. § 315(a)(1)) or that Petitioner is estopped by any prior proceeding before the Office (*see* 35 U.S.C. § 315(e)(1)). Patent Owner's arguments regarding the similarity of prior challenges of the '514 patent are addressed above in our discussion of discretionary denial under 35 U.S.C. § 325(d). *See* Section III.A.

IV. CONCLUSION

After considering the evidence and arguments presented in the Petition and Preliminary Response, we determine that Petitioner has demonstrated a reasonable likelihood that it will succeed on at least one of its challenges to patentability. Accordingly, we institute trial as to all claims and all grounds presented in the Petition. *SAS*, 138 S. Ct. at 1359–60.

V. ORDER

Accordingly, it is

ORDERED that pursuant to 35 U.S.C. § 314(a), an *inter partes* review of claims 1–20 of U.S. Patent No. 8,399,514 B2 is instituted with respect to all grounds set forth in the Petition; and

FURTHER ORDERED that, pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, *inter partes* review of the '514 patent shall commence on the entry date of this Order, and notice is hereby given of the institution of a trial.

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